

- 2 -

Serial No.: 08/702,114

Assistant Commissioner for Patents

1. (Twice Amended) A chimeric fatty body[-pro-]GRF analog with increased biological potency, of the following general formula:

A1-A2-Asp-Ala-Ile-Phe-Thr-A8-Ser-Tyr-Arg-Lys-Val-Leu-  
A15-Gln-Leu-A18-Ala-Arg-Lys-Leu-Leu-A24-Asp-Ile-A27-  
A28-Arg-A30-R<sub>0</sub>

wherein,

A1 is Tyr or His;

A2 is Val or Ala;

A8 is Asn or Ser;

A18 is Ser or Thr;

A15 is Ala or Gly;

A24 is Gln or His;

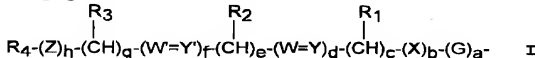
A27 is Met, Ile or Nle;

A28 is Ser or Asp;

A30 is any amino acid sequence of 1 to 15 residues;

R<sub>0</sub> is NH<sub>2</sub>;

wherein A1 is N- [or O-]anchored by a hydrophobic tail of the following general formula I:



wherein,

G is a carbonyl[, a phosphonyl, a sulfonyl or a sulfinyl] group;

X is a oxygen atom, sulfur atom or an amino group (NH);

(W=Y) represents *cis* or *trans* (CH=CR5);

(W'=Y') represents *cis* or *trans* (CH=CR6);

Z is an oxygen or a sulfur atom;

R<sub>1</sub>, R<sub>2</sub>, and R<sub>3</sub>, independently, are selected from [a hydroxyl group,] a hydrogen atom, and a linear or branched C<sub>1</sub>-C<sub>6</sub> alkyl group;

R<sub>4</sub> is [an hydroxyl group,] a hydrogen atom[ or a linear or branched C<sub>5</sub>-C<sub>6</sub> alkyl group];

41-

- 3 -

Serial No.: 08/702,114

Assistant Commissioner for Patents

*C1*  
*Concl'd.*

$R_2$  and  $R_4$ , independently, are a hydrogen atom or a linear or branched  $C_1$ - $C_4$  alkyl group;

a is {0 or} 1;

b is 0 {or} 1;

c is 0 to {8} 3;

d is 0 or 1;

e is 0 to {8} 3;

f is 0 or 1;

g is 0 to {8} 4;

h is 0 {to} 1;

wherein the sum of d + f = 1 or 2 and the sum of a, b, c, d, e, f, g and h is such that the hydrophobic tail of formula I has a linear main chain of between 5 and 7 carbon atoms [(C, O and/or S)].

*2*  
The chimeric fatty body[-pro-]GRF analog of claim 4,  
wherein c is 0.

*3*  
The chimeric fatty body[-pro-]GRF analog of claim 5,  
wherein A30 is Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu.

*4*  
The chimeric fatty body[-pro-]GRF analog of claim 6,  
wherein  $R_0$  is  $NH_2$ .

*5*  
The chimeric fatty body[-pro-]GRF analog of claim 7, of the formula  $cisCH_3-CH_2-CH=CH-CH_2-CO-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-NH_2$  or  $transCH_3-CH_2-CH=CH-CH_2-CO-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Gly-Ala-Arg-Ala-Arg-Leu-NH_2$ .

*42*

Serial No.: 08/702,114

- 4 -

Assistant Commissioner for Patents

9. The chimeric fatty body[-pro-]GRF analog of claim 1, wherein [A] is Tyr or His N-alpha anchored by hydrophobic tail of formula I, wherein  $a = 1$ ; each of  $b$  and  $h = 0$ ; the sum  $d + f = 2$ ; [G = carbonyl;]  $R_1, R_2, R_3$  and  $R_4 =$  hydrogen atom and the sum  $c + e + g = 2, 3$  or  $4$ .

10. The chimeric fatty body[-pro-]GRF analog of claim 1, wherein [A] is Tyr or His N-alpha anchored by hydrophobic tail of formula I, wherein  $a = 1$ ; each of  $b$  and  $h = 0$ ; the sum of  $d + f = 1$  or  $2$ ; G = carbonyl;  $R_1, R_2, R_3$  and  $R_4 =$  hydrogen atom; and the sum  $c + e + g = 3, 4$  or  $5$ .

11. A pharmaceutical formulation for inducing growth hormone release which comprises as an active ingredient a GRF analog as claimed in claim 1 or 2, in association with a pharmaceutically acceptable carrier, excipient or diluent.

12. A method of increasing the level of growth hormone in a patient which comprises administering to said patient an effective amount of a GRF analog as claimed in claim 1 or 2.

13. A method for the diagnosis of growth hormone deficiencies in patients, which comprises administering to said patient a GRF analog as claimed in claim 1 or 2 and measuring the growth hormone response.

14. A method for the treatment of pituitary dwarfism or growth retardation in a patient, which comprises administering to said patient an effective amount of a GRF analog as claimed in claim 1 or 2.

15. A method for the treatment of wound or bone healing in a patient, which comprises administering to said patient an effective amount of a GRF analog as claimed in claim 1 or 2.

43

- 5 -

Serial No.: 08/702,114

Assistant Commissioner for Patents

14  
16. A method for the treatment of osteoporosis in a patient, which comprises administering to said patient an effective amount of a GRF analog as claimed in claim 1 or 14.

15  
17. A method for improving protein anabolism in human or animal, which comprises administering to said human or animal an effective amount of a GRF analog as claimed in claim 1 or 15.

16  
18. A method for inducing a lipolytic effect in human or animal inflicted with clinical obesity, which comprises administering to said human or animal an effective amount of a GRF analog as claimed in claim 1 or 16.

17  
19. A method for the overall upgrading of somatroph function in human or animal, which comprises administering to said human or animal an effective amount of a GRF analog as claimed in claim 1 or 17.

Please add claim 21:

21. (Added) The chimeric fatty body GRF analog of claim 1, 4 of the formula  $\text{transCH}_3\text{-CH}_2\text{-CH=CH-CH}_2\text{-CO-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-NH}_2$ .

Please cancel claims 2, 3, 4 and 20.

44